MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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SUBJECT: One Year Post-Pediatric Exclusivity Post marketing Adverse Event Review: Drug Use Data
Atovaquone/Proguanil hydrochloride (Malarone® and Malarone Pediatric®)
NDA 21-078
Pediatric Exclusivity Approval Date: August 6, 2003

EXECUTIVE SUMMARY

This consult examines drug use for the fixed combination products of atovaquone/proguanil HCL (Malarone® and Malarone Pediatric®) in the pediatric population (0-16 years), with primary focus on patterns of use one year before and one year following the granting of Pediatric Exclusivity on August 6, 2003.

There was an overall increase (~10%) in prescriptions dispensed in the U.S. for the antimalarial class as a whole with an estimated 3.3 million prescriptions dispensed in the 12 month period from August 2001 to July 2002 increasing to an estimated 3.7 million prescriptions dispensed in the 12-month period from August 2003 to July 2004. Single ingredient products accounted for

roughly 94% of the 3.7 million antimalarial prescriptions dispensed from August 2003 to July 2004. Hydroxychloroquine accounted for the majority (~88%) of those dispensed prescriptions. Malarone® and Malarone Pediatric® accounted for roughly 5% and 0.2%, respectively, of the 3.7 million prescriptions dispensed for the antimalarial class in the U.S. from August 2003 to July 2004, dispensed prescriptions for Malarone® appear to have increased approximately 43% from roughly 131,000 prescriptions from August 2002 to July 2003, inclusive, to approximately 187,000 dispensed prescriptions in the 12 months from August 2003 to July 2004, inclusive. During the same two 12-month time periods, dispensed prescriptions for Malarone Pediatric® increased roughly 34.5% from approximately 5,500 to over 7,300 dispensed prescriptions.

Among an insured population in the Caremark system, the pediatric age group (1-16 years) accounted for roughly 4.9% and 96.3% of claims for Malarone® and Malarone Pediatric®, respectively, from August 1, 2003 to July 31, 2004. Applying these percentages from Caremark to the number of prescriptions dispensed from NPA *Plus*™, over 16,000 prescriptions are estimated to have been dispensed in the U.S. to this age group from August 2003 through July 2004.

Pediatricians were responsible for roughly 4% (~7,800 prescriptions) of Malarone® and roughly 40% (~2,900 prescriptions) of Malarone Pediatric® dispensed in the U.S. between August 1, 2003 and July 31, 2004.

INTRODUCTION

On January 3, 2001, Congress enacted the Best Pharmaceuticals for Children Act (BPCA) to improve the safety and efficacy of pharmaceuticals for children. Section 17 of the BPCA requires the reporting of adverse events associated with the use of the drug in children during the one year period following the date when the drug received marketing exclusivity. In support of this mandate, the FDA is required to provide a report to the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee on the drug utilization patterns and adverse events associated with the use of the drug on a quarterly basis. This review is in addition to the routine post-marketing safety surveillance activities the FDA performs for all marketed drugs through the MedWatch program.

Malarone® is a fixed combination oral antimalarial containing 250 mg of atovaquone and 100 mg of proguanil hydrochloride. Malarone Pediatric® contains 62.5 mg of atovaquone and 25 mg of proguanil hydrochloride. Malarone® and Malarone Pediatric® were both approved under NDA 21-078 on July 14, 2000, for the prophylaxis and treatment of *P. falciparum* malaria in adults in areas where resistance to chloroquine has been reported. In the pediatric population, Malarone® and Malarone Pediatric® were approved for: ***Treatment of Malaria:*** The efficacy and safety of MALARONE for the treatment of malaria have been established in controlled studies involving pediatric patients weighing 5 kg or more. Safety and effectiveness have not been established in pediatric patients who weigh less than 5 kg.

Prophylaxis of Malaria: The efficacy and safety of MALARONE have been established for the prophylaxis of malaria in controlled studies involving pediatric patients weighing 11 kg or more. Safety and effectiveness have not been established in pediatric patients who weigh less than 11 kg. Malarone® is commercially available in bottles of 100 tablets and as a unit dose pack of 24 tablets. Malarone Pediatric® is available in bottles of 100 tablets.

The Pediatric Exclusivity Board of the FDA granted pediatric exclusivity for both Malarone® and Malarone Pediatric® (NDA 02-1078) on August 6, 2003

We will use the term Malarone® and Malarone Pediatric® to refer to the adult tablet or the pediatric tablet unless otherwise specified. To date, there are no generic competitors of this product.

This review describes outpatient drug usage of Malarone® and Malarone Pediatric® in the pediatric population as compared to the adult population. Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

DATA SOURCES

Sales data reflecting the number of bottles and tablets sold by the manufacturer to various retail and non-retail channels of distribution were analyzed using IMS Health's National Sales Perspectives™ database. Because 86% of these products were sold to retail outpatient settings from August 2003 to July 2004, we focused our review to examine this category of product utilization. (Table 1). Clinics represent an additional 5% of sales, however, the FDA currently does not have access to data that would capture drug use in the outpatient clinic setting. Outpatient Malarone® dispensed prescriptions were measured using IMS Health's National Prescription Audit *Plus*™ [NPA *Plus*™] combined with prescription claims data from Caremark [Dimension Rx™]. There were no inpatient claims for Malarone® in the drug use databases licensed by the FDA at the time of this consult

Table 1: Sales of Bottles (Eaches) and Tablets (Extended Units) Sold Through Retail and Non-Retail Channels of Distribution During August 2003 – July 2004 in IMS Health, National Sales Perspectives™

		August 2003 – July 2004			
		Eaches	%	Extended Units	%
All Atovaquone/Proguanil (Malarone® and Malarone Pediatric®)		**131,000**	***100.0%***	**6,437,000**	***100.0%***
Retail		**115,300**	***88%***	**5,525,000**	***85.8%***
	Chain Stores	79,700	*60.8%*	3,556,000	*55.2%*
	Independent	183,00	*13.9 %*	916,000	*14.2%*
	Food Stores	15.100	*11.5%*	851,000	*13.2%*
	Mail Service	2,200	*1.7%*	202,000	*3.1%*
Non-Retail		**15,800**	***12%***	**912,000**	***14.2%***
	Clinics	6,500	*4.9%*	350,000	*5.4%*
	Miscellaneous - Prisons	2,600	*2%*	115,000	*1.8%*
	Federal Facilities	2,100	*1.6%*	184,000	*2.9%*
	Non-Federal Facilities	1,300	*1%*	62,000	*1%*
	HMO	1,100	*0.9%*	43,000	*0.7%*
	Miscellaneous-Universities	900	*0.7%*	76,000	*0.7%*
	Long Term Care	800	*0.6%*	36,000	*0.6%*
	Home Health Care	500	*0.4%*	43,000	*0.7%*
	Miscellaneous-Other	0	*0%*	3,000	*0%*

National Sales Perspectives™ Retail and Non-Retail, Moving Annual Total: August 2003 – July 2004, Data Extracted October 2004.
Original File: 0410mal4.dvr

I. OUTPATIENT DRUG USE

IMS HEALTH, NATIONAL PRESCRIPTION AUDIT PLUS™ (NPA PLUS™)

NPA Plus™ measures the retail dispensing of prescriptions, or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. These retail pharmacies include chain, independent, food store, mail order, discount houses, and mass merchandiser pharmacies, as well as nursing home (long-term care) pharmacy providers. With the exception of the long-term care and mail order pharmacy settings, information on the specialty of the prescribing physician is included in this database.

The number of dispensed prescriptions is obtained from a sample of approximately 22,000 pharmacies throughout the U.S. and projected nationally. The pharmacies in the database account for approximately 40% of all pharmacy stores and represent approximately 45% of prescription coverage in the U.S.

Data for this analysis included all prescriptions dispensed from August 1, 2001 to July 31, 2004, inclusive.

CAREMARK DIMENSION RX™

Caremark is one of the largest pharmacy benefit manager (PBM) companies in the US, currently covering over 75 million patient lives, and processing over 450 million prescription claims annually. Patients whose claims are processed by Caremark are covered under various types of insurance plans, including health maintenance organizations (HMOs), employers' self-insured health plans, selected managed care plans, and other selected traditional health insurers. Caremark represents patients from all 50 states and includes special populations such as the elderly, children, and women of childbearing age. The representativeness of those included in the Caremark system to all persons receiving dispensed prescriptions in the U.S. is not known however.

For this analysis, prescription claims in the Caremark system were examined from August 1, 2002 to July 31, 2004, inclusive.

RESULTS

I. Dispensed Prescriptions

Dispensed prescriptions for both Malarone® products appear to have increased approximately 42% from roughly 136,500 dispensed prescriptions from August 2002 to July 2003, inclusive, to over 194,000 prescriptions dispensed in the 12–month period from August 2003 to July 2004, inclusive (Table 2). Dispensed prescriptions for Malarone Pediatric® appear to have increased approximately 34.5% from roughly 5,500 in the period from August 2002 to July 2003, inclusive, to over 7,400 prescriptions in the 12 months from April 2003 to March 2004, inclusive (Table 2). Malarone® and Malarone Pediatric® accounted for approximately 5% and 0.2%, respectively, of the estimated 3.7 million prescriptions dispensed for all antimalarials (USC3 16000) in the U.S. from August 1, 2003 through July 31, 2004 (Table 2).

Table 2: Total Number of Prescriptions Dispensed in Retail Pharmacies Nationwide for Antimalarial Products (USC 3-16000)

	Moving Annual Total					
	Aug 2001-Jul 2002		Aug 2002-Jul 2003		Aug 2003-Jul 2004	
	N	(%)	N	(%)	N	(%)
All Products	**3,331,864**	***100.0%***	**3,453,297**	***100.0%***	**3,661,481**	***100.0%***
PLAIN	**3,239,036**	***(97.2%)***	**3,316,133**	***(96%)***	**3,466,477**	***(94.7%)***
Hydroxychloroquine	**2,817,120**	***(87%)***	**2,926,504**	***(88.3%)***	**3,466,477**	***(87.8%)***
Mefloquine	**298,841**	***(9.2%)***	**256,026**	***(7.7%)***	**271,588**	***(7.8%)***
Chlorquine	**98,537**	***(3%)***	**109,875**	***(3.3%)***	**129,717**	***(3.7%)***
Pyrimethamine	**21,166**	***(0.7)***	**21,118**	***(0.6%)***	**19,210**	***(0.6%)***
Primaquine	**2,839**	***(0.1%)***	**2,563**	***(0.1%)***	**2,971**	***(0.1%)***
Quinacrine	**33**	***(0%)***	**47**	***(0%)***	**75**	***(0%)***
Halofantrine						
COMBINATION PRODUCTS	**92,828**	***(2.8 %)***	**137,164**	***(4%)***	**195,004**	***(5.3%)***
Atovaquone/Proguanil (GSK)	**92,027**	***(99.1%)***	**136,470**	***(99.5%)***	**194,289**	***(99.6%)***
Malarone 250/100	**88,175**	***(95.8%)***	**130,950**	***(96%)***	**186,924**	***(96.2%)***
Malarone Pediatric 62.5/25	**3,852**	***(4.2%)***	**5,520**	***(4%)***	**7,365**	***(3.8%)***
Sulfadoxine/Pyrimethamine	**801**	***(0.9%)***	**694**	***(0.5%)***	**714**	***(0.4%)***
Primaquine/Choroquine		***(0.0%)***		***(0.0%)***		***(0.0%)***

IMS Heath, National Prescription Audit *Plus*™, Moving Annual Totals Aug 2001- Jul;y2004, Extracted Oct 2004.
Original file: 0410mal1.dvr

The top three prescriber specialties for Malarone® from August 2003 through July 2004 were internal medicine (25.8%), family practice (17.7%), and infectious disease (14.7%); pediatricians accounted for only 4% of those dispensed prescriptions. During the same 12-month time period, pediatricians were the top prescribers of Malarone Pediatric®, accounting for roughly 40% of dispensed prescriptions for this product followed by family practice (11.4%), internal medicine (10.4%), infectious disease (8.9%) (Table 3).

Table 3: Total Number of Prescriptions Dispensed by Specialty Nationwide for Malarone® and Malarone Pediatric®
***excludes Long Term Care and Mail Order channels**

	Year					
	Aug 2001-Jul 2002		Aug 2002-Jul 2003		Aug 2003-Jul 2004	
	N	(%)	N	(%)	N	(%)
PRODUCT BY MD SPECIALTY	**89,278**	***100.0%***	**132,453**	***100.0%***	**188,779**	***100.0%***
Malarone 250mg/100mg	**85,523**	***(95.8%***	**127,106**	***(96%)***	**181,627**	***(96.2%)***
Internal Medicine	19,845	*(23.2%)*	32,188	*(25.3%)*	46,796	*(25.8%)*
Family Practice	13,946	*(16.3%)*	21,568	*(17%)*	32,175	*(17.7%)*
Infectious Disease	13,708	*(16%)*	18,784	*(14.8%)*	26,772	*(14.7%)*
Unknown	6,429	*(7.5%)*	98,900	*(7%)*	11,481	*(6.3%)*
Osteopathic Medicine	4,473	*(5.2%)*	6,357	*(5%)*	8,861	*(4.9%)*
Pediatrics	**3.485**	***(4.1%)***	**5,688**	***(4.5%)***	**7,864**	***(4.3%)***
Total Others (62)	23,637	*(27.7%)*	33,631	*(26.5%)*	47,678	*(26.3%)*
Malarone Pediatric 62.5mg/25mg	**3,755**	***(4.2%)***	**5,347**	***(4%)***	**7,152**	***(3.8%)***
Pediatrics	**1,304**	***(34.7%)***	**2,104**	***(39.3%)***	**2,892**	***(40.4%)***
Family Practice	532	*(14.2%)*	699	*(13.1%)*	814	*(11.4%)*
Internal Medicine	308	*(8.2%)*	497	*(9.3%)*	745	*(10.4%)*
Infectious Disease	347	*9.2%)*	451	*(8.4%)*	635	*(8.9%)*
Unknown	293	*(7.8%)*	340	*(6.4%)*	437	*(6.1%)*
Total Others (51)	971	*(25.9%)*	1256	*(23.5%)*	1,629	*(22.8%)*

IMS Heath, National Prescription Audit *Plus*™, Moving Annual Totals: Aug 2001-July 2004, Data Extracted October 2004.
Original file: 0410mal3.dvr

II. Patient Demographics

Among a large, insured patient population managed by Caremark, approximately 4.9% of processed claims for Malarone® and 96.3% of claims for Malarone Pediatric® were for persons aged 1-16 years from July 2003 through August 2004 (Table 4).

Total Malarone® claims increased approximately 50% (from 20,843 to 31,171 claims) between the two 12-month time periods, August 2002 – July 2004. Pediatric claims for all Malarone® products increased roughly 71% from (1,520 to 2,594 claims) during the same two 12-month time periods.

Table 4: Total Number of Paid Prescription Claims for Malarone® and Malarone Pediatric® From Caremark Pharmacy Benefit Manager Database.

	Moving Annual Total					
	Aug 2001-Jul 2002		Aug 2002-Jul 2003		Aug 2003-Jul 2004	
# CLAIMS BY PRODUCT	N	(%)	N	(%)	N	(%)
TOTAL	**14,197**	***100.0%***	**20,843**	***100.0%***	**31,171**	***100.0%***
Malarone 250mg/100mg	**13,658**	***(96.2%)***	**20,113**	***(96.5%)***	**30,011**	***(96.3%)***
Peds (1-16 yrs)	**657**	***(4.8%)***	**842**	***(4.2%)***	**1,477**	***(4.9%)***
Adults (17+ yrs)	**13,001**	***(95.2%)***	**19,271**	***(95.8%)***	**28,354**	***(95.1%)***
Malarone Pediatric 62.5mg/25mg	**539**	***(4.2%)***	**730**	***(4%)***	**1,160**	***(3.8%)***
Peds (1-16 yrs)	**501**	***(92.9%)***	**678**	***(92.9%)***	**1,117**	***(96.3%)***
Adults (17+yrs)	**38**	***(7.1%)***	**52**	***(7.1%)***	**43**	***(3.7%)***

Caremark Dimension Rx, Data Extracted October , 2004.

Since NPA Plus™ does not include complete historical demographic information on patients, we applied the proportions for demographic subgroups from Caremark data to the NPA Plus™ data to approximate the number of Malarone® prescriptions dispensed nationwide to children. Specifically, we applied the proportion of pediatric claims for Malarone® and Malarone Pediatric®, 4.9% and 96.3% respectively (from Caremark, Table 4) to 186,924 and 7,365 dispensed prescriptions for these products (from NPA Plus, Table 2). Using this approach, approximately 9,159 Malarone® and 7,092 Malarone Pediatric® prescriptions are estimated to have been dispensed for persons aged 1-16 years in the U.S. from August 1, 2003 to July 31, 2004 (Table 5).

Table 5: Estimated Nationwide Prescriptions Dispensed for all Malarone during August 2003 – July 2004 by Age Group (1-16)			
	August 2003 – July 2004		
Age 1-16	Total Number of Prescriptions* Dispensed for All Age Groups (*From Table 2*)	% Pediatric Claims** (Ages 1-16 yrs.) (*from Table 4*)	Estimated Number of Prescriptions Dispensed to the Pediatric Population (Ages 1-16 yrs)
Malarone®	**186,924**	**4.9%**	**9,159**
Malarone Pediatric®	**7,365**	**96.3%**	**7,092**
Total	**194,289**	**n/a**	**16,251**

*IMS Heath, National Prescription Audit *Plus*™, Moving Annual Totals: Aug 2001-July 2004, Data Extracted October 2004.
Original file: 0410mal3.dvr
**Caremark Dimension Rx, Extracted October 2004

LIMITATIONS

NPA Plus™ data provide an estimate of the total number of prescriptions dispensed in the U.S. However, NPA Plus™ does not include complete historical demographic information, such as age and gender. The inclusion of prescriber specialty data in this report does not include mail order and long-term care channels. However, these channels accounted for less than 4% of the overall prescriptions dispensed (data not shown).

Caremark data cannot be projected to make national level estimates of use, but its large sample size can provide use estimates for even less commonly used products. Although the data from Caremark may not be nationally representative, they provide a useful description of prescription drug use in the U.S. for a large proportion of the population with prescription drug coverage. Estimates of the number of prescriptions dispensed nationally to pediatric populations based upon the proportion dispensed to pediatric patients in the Caremark system are dependent upon the assumption that the patterns identified in Caremark data are similar across populations with and without prescription drug coverage. Reliable information for patients less than the age of 1 year is not available from this data source.

CONCLUSION

This consult examines drug use for Malarone® in the pediatric population (1-16 years), with primary focus on patterns of use one year before and one year following the granting of Pediatric Exclusivity on August 6, 2003. Comparing data from the year prior to exclusivity with that following exclusivity, there was an overall increase of approximately 10% in prescriptions dispensed in the U.S. for the antimalarial class as a whole. An estimated 3.3 million prescriptions were dispensed in the 12-month period August 2001 - July 2002, increasing to an estimated 3.7

million prescriptions dispensed in the 12-month period August 2003 - July 2004. Single ingredient products accounted for the roughly 94% of the 3.7 million antimalarial prescriptions dispensed from August 2003 to July 2004, with hydoxychloroquine accounting for the great majority (88%). Malarone® and Malarone Pediatric® accounted for a small proportion (roughly 5% and 0.2%, respectively) of the 3.7 million prescriptions dispensed in the U.S. from August 2003 and July 2004. Dispensed prescriptions for Malarone® appear to have increased 43% from roughly 131,000 pre-exclusivity period to approximately 187,000 post-exclusivity period. Across the same two 12-month time periods, dispensed prescriptions for Malarone Pediatric® increased roughly 34.5% from approximately 5,500 to over 7,300 dispensed prescriptions. By applying the percentages of pediatric claims from Caremark data to dispensed prescription data from NPA *Plus*™, we estimate that over 16,000 prescriptions for Malarone® and Malarone Pediatric® were dispensed in the U.S. to persons aged 1-16 years from August 2003 through July 2004.

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